INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/20746

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claim Nos.: 51-64
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-50 (SEQ ID NO: 1 and 2)

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/20746

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A01N 63/00; A61K 48/00
US CL : 424/93.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/93.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARGARITIS et al. Long-term expression of activated FVII in vivo following AAV-mediated liver gene transfer: Implications for treatment with continuous infusion of recombinant activated FVII. Blood. November 2001, Vol 98. No. 11 Part 1, page 696a, abstract 2908.	1, 2, 18, 26, 36-42, 45-50
X	US 6,132,729 A (THORPE et al) 17 October 2000 (17.10.2000), see whole document, especially columns 7-10 and 33.	1-17, 26-36, 38-40, 45-50
Y,E	US 2003/0228282 A1 (GAO et al) 11 December 2003 (11.12.2003), see whole document, especially pages 5-12.	1-50
Y,E	US 2003/0013189 A1 (WILSON et al) 16 January 2003 (16.01.2003) see whole document, especially pages 4-6.	24, 25

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
21 September 2005 (21.09.2005)

Date of mailing of the international search report
14 NOV 2005

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

PCT/US03/[illegible]46

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-50, drawn to a recombinant adeno-associated viral (AAV) vector comprising a nucleic acid set forth in SEQ ID NO: 1 or a nucleic acid encoding a human Factor VII peptide set forth in SEQ ID NO: 2.

Group II, claim(s) 1-9, 11-16, 18-30, and 36-50, drawn to a recombinant adeno-associated viral vector comprising a nucleic acid set forth in SEQ ID NO: 7 or a nucleic acid encoding a rat Factor VII peptide set forth in SEQ ID NO: 8.

Group III, claim(s) 1-9, 11-16, 18-30, and 36-50, drawn to a recombinant adeno-associated viral vector comprising a nucleic acid set forth in SEQ ID NO: 9 or a nucleic acid encoding a danio Factor VII peptide set forth in SEQ ID NO: 10.

Group IV, claim(s) 1-9, 11-16, 18-30, and 36-50, drawn to a recombinant adeno-associated viral vector comprising a nucleic acid set forth in SEQ ID NO: 11 or a nucleic acid encoding a murine Factor VII peptide set forth in SEQ ID NO: 12.

Group V, claim(s) 1-9, 11-16, 18-30, and 36-50, drawn to a recombinant adeno-associated viral vector comprising a nucleic acid set forth in SEQ ID NO: 13 or a nucleic acid encoding a chicken Factor VII peptide set forth in SEQ ID NO: 14.

Group VI, claim(s) 1-9, 11-16, 18-30, and 36-50, drawn to a recombinant adeno-associated viral vector comprising a nucleic acid encoding a rabbit Factor VII peptide set forth in SEQ ID NO: 15.

Group VII, claim(s) 1-9, 11-16, 18-30, and 36-50, drawn to a recombinant adeno-associated viral vector comprising a nucleic acid encoding a bovine Factor VII peptide set forth in SEQ ID NO: 17.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I:
I) SEQ ID NO: 3 and 4; and
II) SEQ ID NO: 5 and 6.

The claims are deemed to correspond to the species listed above in the following manner:

I) claims 3-8, 11-16, 27-30; and
II) claims 3-8, 11-16, 27-30.

The following claim(s) are generic: claims 1, 2, 9, 18-26, and 36-50.

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking Groups I-VII appears to be that they all relate to an AAV vector comprising a nucleic acid encoding a Factor VII peptide.

However US 5,789,390 (4-8-98) teaches an AAV vector comprising a nucleic acid encoding Factor VII peptide.
Therefore, the technical feature linking the inventions of Groups I-VII does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of group I is considered to be SEQ ID NO: 2.

The special technical feature of group II is considered to be SEQ ID NO: 8.
The special technical feature of group III is considered to be SEQ ID NO: 10.
The special technical feature of group IV is considered to be SEQ ID NO: 12.
The special technical feature of group V is considered to be SEQ ID NO: 14.
The special technical feature of group VI is considered to be SEQ ID NO: 15.
The special technical feature of group VII is considered to be SEQ ID NO: 17.

Accordingly, Group I-VII are not so linked by the same or a corresponding technical feature as to form a single general inventive concept.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: I) each variant has a different mode of action; and II) each variant has a different mode of action.

Continuation of B. FIELDS SEARCHED Item 3:
WEST, STN
search terms: AAV, Factor VII, FVII, hemophilia, adeno associated virus

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." **or**
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

cytomegalovirus immediate-early promoter/enh[illegible]HD-CMV-FVIII), or a tissue-specific promoter comprising the proximal human FVIII promoter with an upstream Hepatocyte Nuclear factor 1 concatemer (HD-HNF-FVIII). Experimentation with these vectors has been carried out in hemophilia A mice. The genetic background of the mouse population consists of outbred crosses between C57BL/6 and Balb/c mice. We have performed these crosses to control for limitations in immune responsiveness known to affect similar studies using inbred strains. Vector dosing has ranged from $5x10^{10}$ to $1x10^{12}$ viral particles (vp) per mouse. No liver toxicity has been detected by alanine transaminase (ALT) measurement at any of the doses administered. However, early onset inflammation, measured by IL-6 levels, was dose dependent, but vector-independent, with levels at 5 hours increasing when doses higher than $1x10^{11}$ were delivered, and reaching as high as 7284 pg/ml in mice receiving $1x10^{12}$ vp/mouse. One stage FVIII assays, employing pooled normal mouse plasma as a standard, were used to determine FVIII levels. Our results indicate that both vectors are capable of mediating short-term elevations in FVIII, but only those mice treated with the tissue-specific HD-HNF-FVIII vector show long-term correction, extending beyond 5 months. Hemophilic animals treated with HD-CMV-FVIII exhibited FVIII levels as high as 3440 mU/mL (normal = 1000 mU/mL) by 1 week after vector administration, however, by week 2, FVIII levels in all animals treated with this vector had returned to pre-treatment values, around 100 mU/mL. Detection of anti-canine FVIII antibodies correlated with decreased FVIII levels in all of these animals. Inhibitor onset began at 2 weeks, corresponding to the drop in FVIII, and rose to 1200 Bethesda Units (BU) by week 16. Inhibitor levels, although decreasing, have persisted to 6 months post- treatment. In contrast, we have been able to demonstrate long-term FVIII correction in hemophilic mice administered the HD-HNF-FVIII vector. As with mice treated with the HD-CMV-FVIII vector, FVIII levels were highest between 48hrs and 1 week after initial treatment, peaking at up to 6000 mU/mL, and subsequently declining by week 3. In 6 of 16 mice, treated with the HD-HNF-FVIII vector, FVIII was sustained at levels over 200mU/mL for 12 - 20 weeks. In the remaining mice, levels dropped below 100mU/mL and anti-FVIII inhibitors were detected. Long-term expression appears to be dose-independent, except at the highest dose of $1x10^{12}$ vp/mouse where none of the mice demonstrated expression beyond week 3. Although we have yet to conclusively determine why some mice show sustained expression, and others do not, we suspect vector induced inflammation may play a role in dendritic cell and macrophage recruitment leading to the development of anti-FVIII immunity. In addition to mouse studies, we have also begun experimentation with the hemophilia A dog colony housed at Queens University. Early results from a single dog injected with $5x10^{11}$vp/kg did not show any increase in FVIII levels or a change in whole blot clot times. No liver, kidney, or muscle toxicity was detected, and platelet counts remained normal. Further studies with the dogs are set to continue using higher vector doses.

Abstract# 2908 **Poster Board #-Session: 893-III**

Long-Term Expression of Activated FVII In Vivo Following AAV-Mediated Liver Gene Transfer: Implications for Treatment with Continuous Infusion of Recombinant Activated FVII. Paris Margaritis*, Valder R. Arruda, Katherine A. High. *Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, USA.*

A current treatment for acute bleeding episodes in hemophilia A and B patients who have developed inhibitory antibodies to the infused factor (factor VIII and factor IX, respectively), is administration of high doses of recombinant activated human factor VII (rFVIIa). While repeated bolus injections of rFVIIa have been used, experience with continuous infusion of rFVIIa is limited and raises safety concerns regarding occlusive vascular complications resulting from activation of the coagulation system. Here, we investigated the effect of long-term continuous expression of FVIIa in mice at various circulating levels, as part of a gene therapy strategy for treatment of hemophilic animals with inhibitors. We engineered a FVII variant that is *intracellularly*-processed and secreted as activated FVII (FVIIa), by inserting a protein recognition sequence for an intracellular protease at position Arg 152-Ile 153. This FVII variant is predominantly secreted *in vitro* in a double chain, activated FVII form and has similar *in vitro* activity and *in vivo* half-life as recombinant FVIIa, following injection in normal C57BL/6 mice. In order to demonstrate the efficacy of our gene transfer approach, we initially used rFVIIa into hemophilia A and B mice with and without inhibitors, injected at the clinically effective dose of 90 micrograms/kg. We observed a shortening of the prothrombin time (an assay sensitive to FVIIa levels) as early as 15 min, which returned to baseline after 6 hours, indicating that our approach can be used in a hemophilic mouse model. To further study the long-term effect of continuous FVIIa expression, we constructed a recombinant AAV-2 viral vector carrying this FVIIa transgene under the control of a liver-specific promoter and injected vector into the portal circulation in hemostatically normal immunodeficient mice (n=7) at doses ranging from 1.5×10^{11} vector genomes (v.g.)/mouse to 2.4×10^{12} v.g./mouse. Mouse plasma was collected and assayed for antigen levels by an ELISA specific for human FVII/FVIIa. Following gene transfer, we observed stable, long-term expression of FVIIa with antigen levels ranging from 150 ng/ml to 950 ng/ml, as assayed over a period as long as 24 weeks post-injection. Throughout the course of these experiments, we did not observe any adverse effects at any doses tested. To further investigate any changes in the activity of the coagulation system in these animals, we assayed plasma samples collected at time points up to 24 weeks for the presence of elevated levels of thrombin-antithrombin III (TAT) complexes. By using an ELISA for TAT that is known to cross-react with murine proteins, we observed TAT levels ranging from 0.8 ng/ml to 20.1 ng/ml, while TAT levels in normal animals were approximately 22 ng/ml. This indicates that the long-term expression of the FVIIa transgene did not result in detectable changes in the mouse coagulation system. Overall, we show that long-term expression of FVIIa can be achieved by AAV gene transfer without thrombotic complications. More extensive testing will be required to demonstrate the efficacy of such therapeutic strategy in hemophilic animals with inhibitors. These data support the potential of such an approach for hemophilic patients with inhibitors.

Abstract# 2909 **Poster Board #-Session: 894-III**

Polyclonal Ex Vivo Transduction in Successful SCID-X1 Gene Therapy. Manfred Schmidt*,[1] Marina Cavazzana-Calvo,[2] Salima Hacein-Bey*,[2] Francoise LeDeist*,[2] Nina Lemke*,[1] Manuela Wissler*,[1] Alain Fischer*,[2] Christof von Kalle.[1,3] *[1]Internal Medicine I, University of Freiburg, Freiburg, Germany; [2]Unite d'Immunologie et d'Hematologie Pediatriques, Hopital Necker, Paris, France; [3]Molecular Medicine and Cell Research, University of Freiburg, Freiburg, Germany.*

Oncoretroviral gene transfer into T cells, cord blood or marrow cells has been used to correct genetic defects in cells from patients with potentially fatal human severe combined immunodeficiency disease (SCID) of different genetic origin [Blaese, 1995; Hoogerbrugge, 1996; Bordignon, 1995; Kohn, 1995; Misaki, 2001]. Clinical T cell function could be restored to normal in 4 of 5 children with SCID-X1 by transplantation of bone marrow genetically corrected with human IL-2-receptor gamma chain (IL-2Rg) cDNA [Calvazzana-Calvo, 2000]. The clinical success of this trial suggests that expression of the corrective transgene reconstitutes growth to many lymphoid cell clones, and potentially also to their precursors. TCR Vβ usage has suggested that the T cell repertoire in these patients is indeed polyclonal. It has remained unclear however, whether these have developed from many or few precursors, because non-lymphoid cells derive no known growth advantage from the transgene. Here we show by LAM-PCR, that in this SCID-X1 gene therapy trial, multiple clones have formed transgene corrected lymphoid hematopoiesis (3 of 4 patients analyzed, each T cell and PBMC sample revealing 20 to 40 LAM-PCR amplicons). High resolution integration site analysis indicates on single clones that transgene integration was mostly distributed as one copy per cell. The detection of multiple different integration sites in the peripheral blood indicates that transgene correction has been achieved in a polyclonal cell population in this trial despite the unconditioned engraftment and transgene-related clonal selection pressure. As indicated by the analysis of peripheral blood granulocytes (3 of 4 patients, 1 to 3 LAM-PCR amplicons detected), the identification of integration sites in sorted myeloid colonies will enable us to study whether this integration occurred at least in part into pluripotent hematopoietic stem or progenitor cells that contributed to both myeloid and lymphoid lineages. Counting and tracking of hematopoietic progenitor and stem cells in vivo is possible, yields decisive and surprising information on the biology of hematopoiesis and should be a component of every preclinical and clinical gene transfer study using integrating vector systems.

Abstract# 2910 **Poster Board #-Session: 895-III**

Lentiviral Mediated Systemic Antiangiogenic Therapy for High-Grade Non-Hodgikin Lymphoma. Koichi Miyake, Noriko Suzuki*, Takashi Shimada. *Department of Biochemistry and Molecular Biology, Division of Gene Therapy Research Center for Advanced Medical Technology, Nippon Medical School, Tokyo, Japan.*

Since growth of solid tumors depends on the generation of new blood vessels, it was proposed that antiangiogenic therapy may effective to induce tumor dormancy and stabilization. In hematopoietic malignancies, it has been also reported that expression of VEGF and related receptors Flt-1 and FLK-KDR is important for development of most B-cell malignancies. An antiangiogenic drug, thalidomide, was found to be effective in patients with refractory myeloma. In addition, remodeling and immature vessels were observed in biopsy specimens of high-grade non-Hodgikin lymphoma (NHL), and high circulating levels of VEGF and b-FGF were found to correlate with a poor prognosis in patients with NHL. To evaluate the effect of the antiangiogenic gene therapy for NHL, we constructed VSV pseudotyped lentiviral vectors expressing angiostatin (VSV-A), endostatin (VSV-E), and GFP (VSV-G). A model of human NHL was generated by intraperitoneal transplantation of 1×10^7 Namalwa cells derived from an Epstein-Barr virus-positive Burkitt NHL into 6 to 8-week-old nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice. Visible and measurable tumors were observed beginning on day 10 after transplantation. A single injection of the lentiviral vectors (1×10^8 TU/ml) was given into right quandriceps muscles of the NHL mice. It was confirmed that lentiviral vectors containing both central polypurine tract and posttranscriptional element were highly efficient in transducing terminally differentiated muscles and stably expressing the transgene. ELISA assay showed that the concentration of endostatin in plasma was increased after VSV-E injection. Tumor growth was significantly inhibited in mice injected with VSV-A or VSV-E, but not VSV-G. On day 28, mean tumor volumes in mice treated with VSV-A and VSV-E were reduced by 20% and 55%, respectively. Moreover, combination of VSV-A and VSV-E vectors resulted in 70% reduction of tumor mass. The survival effect was also observed in mice injected with VSV-A, VSV-E, or VSV-A + VSV-E. These results indicate that lentiviral mediated systemic antiangiogenic therapy is highly promising for treatment of high-grade NHL.

Abstract# 2911 **Poster Board #-Session: 896-III**

Bone Marrow Derived Mesenchymal Stem Cells Serve as Precursors for Stromal Fibroblasts in Malignant Tumors and Show Potential for Cancer Therapy. Matus Studeny*,[1] Frank C. Marini*,[1] Claudia Zompetta*,[1] Richard E. Champlin,[1] Isaiah J. Filder,[2] Michael Andreeff.[1] *[1]Blood and Marrow Transplantation, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [2]Cancer Biology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA.*

Stromal fibroblasts in solid tumors are believed to originate from resident precursor cells at the tumor sites. However, recent reports suggest that bone marrow derived mesenchymal stem cells (MSC) can represent a systemic source for maintenance and renewal of non-hematological cells in organs remote from the bone marrow. Importantly, increased cells turnover and tissue remodeling may be essential for successful engraftment of MSC at sites other than bone marrow. We investigated whether MSC could serve as progenitors of stromal fibroblasts in tumors and whether they can be used for the production of anti-cancer agents at the site of neoplasms. We here demonstrate that human MSC contribute to the